PATENT

0020-4491P

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Kyogo ITOH et al

Serial Number:	09/202,047	Group:	1642
Filed:	December 7, 1998	Examiner:	Sheela Huff

For: Tumor Antigen Proteins, Genes Therefor, and Tumor Antigen Peptides

DECLARATION UNDER 37 C.F.R. § 1.132

Dear Sir:

The undersigned, Kyogo Itoh, M.D., Ph.D., hereby declares and states as follows:

1. My Curriculum Vitae including a list of my publications and credentials, is attached hereto as Appendix A.

2. On the basis of the qualifications set forth in my Curriculum Vitae, I submit that I am an expert in the fields of molecular biology and oncology. I have long been engaged in research on tumor antigens and identified several novel tumor antigens such as SART-2, SART-3, Cyclophilin B, and ART-1 in addition to SART-1 as the subject matter of the present invention.

3. I have studied the Office Action issued on February 1, 2001 and understood what is the essence of the Office Action.

4. I am the primary inventor of the US Patent Application number 09/202,047 (hereinafter, "present application") and am familiar with the scientific and practical significance of the invention. I am also familiar with cited Nakao et al,

Cancer Res. 55: 4248-4252, October 1, 1995 (hereinafter, "Nakao et al") as one of co-authors.

5. In my capacity as set forth above, I would like to express my opinion on the Office Action especially on the following issues:

1) Claims 7 and 8 meets the requirements under 35 USC § 112; and
2) Claims 6-9 and 12-13 are novel over Nakao et al

5.1. Claims 7 and 8 meets the Disclosure Requirements

5.1.1. The amended claims 7 and 8 read:

Claim 7: *An isolated tumor antigen peptide consisting of part of the protein of claim 6, which binds to MHC class I antigen to be recognized by CTLs.*

Claim 8: *An isolated tumor antigen peptide of claim 7 which comprises the amino acid sequence of positions 749-757, 736-744, 785-793, or 690-698 in the amino acid sequence of SEQ ID NO: 1.*

The Examiner stated as follows:

"The specification fails to enable any peptides that are produced through "intracellular decomposition" which bind MHC class I antigen and can be recognized by T cells..."

However, one of ordinary skill in the art could make and use the peptides as claimed in claims 7 and 8 above on the basis of the description, teaching, and guidance in the specification in view of the technical background at the filing date of the priority application of the present application (June 7, 1996, hereinafter, "priority date").

5.1.2.The present invention is based on the successful cloning of a novel tumor antigen protein, which is now called "SART-1". Before the priority date, there had

been no tumor antigens identified other than those originated from a special tumor, i.e., melanoma. Accordingly, it was very much desired a tumor antigen protein to be isolated from more common tumors such as squamous cell carcinoma (see, page 7, line 1 through page 8, line 22 of the specification). The present inventors, for the first time, succeeded in the cloning and the characterization of a novel tumor antigen protein (SART-1) from a tumor other than melanoma, that is, squamous cell carcinoma derived from esophageal cancer. J. Exp. Med., one of most famous learned journals, published our research results regarding cloning and characterization of SART-1 in recognition of the significance. See, Appendix B (*J. Exp. Med.* **187**: 277-288, 1998).

5.1.3. The cloning of SART-1 was extremely difficult. In the absence of any genetic information, we, the inventors, had to use the expression cloning technique, which comprises expressing randomly an enormous numbers of cDNA clones, determining the activity of each clone, and selecting the intended clone(s). We repeated the procedures again and again and finally isolated one cDNA clone from squamous cell carcinoma derived from esophageal cancer, as described in Examples 1 to 3 of the present application. The clone is referred to as "K3" in the present specification and now known as "SART-1". We then confirmed that the gene encoding SART-1 (K3), when transformed into a cell, yields a peptide fragment(s) through the intracellular processing of SART-1, which fragment binds to major histocompatibility complex (MHC) class I antigen, i.e., HLA antigen, and is recognized by cytotoxic T lymphocytes (CTLs), as recited in claim 6. These results are shown in Table 2 in Example 3 of the present specification. In Table 2, the activity of SART-1 (K3) is determined by measuring the amount of IFN-γ generated by CTLs. It is known that CTL produces IFN-γ only when it recognizes a peptide presented by MHC class I antigen (HLA antigen), which peptide have been generated through the intracellular processing, and hence the results in Table 2 certainly prove that "an isolated protein" of the present invention as defined in claim 6 has the activity as recited in the said claim.

5.1.4. As mentioned above, the cloning of SART-1 could not be achieved without resolving considerable difficulties. Once the tumor antigen protein was cloned and identified, the next step for determining a part (portion) thereof having an

activity as a tumor antigen peptide could be carried out by a technique known in the art.

5.1.5. It was commonly known in the art that antigen peptides which are bound and presented by MHC class I antigen (HLA antigen) are generally 8-12 amino acid long. For example, antigen peptides listed in *Immunogenetics*, **41**:178-228, 1995 are all have amino acid sequences of 8 to 12 amino acids. See, Table. Likewise, *J. Immunol.*, **152**:3913, 1994 (see, abstract) and *J. Immunol.*, **152**:3904, 1994 also describes the requisite amino acid length of antigen peptide presented by MHC class I antigen (HLA antigen) to be 8-12 a.a. and 8-11 a.a., respectively. These publications have been filed with the USPTO as IDS.

5.1.6. Further, it was also known that, regarding some MHC class I antigens such as HLA-A24, there is a rule (motif) in the amino acid sequence of a peptide to be presented thereby. Accordingly, one could even identify a tumor antigen peptide based on a peptide sequence comprising the motif. The state of art at the priority date is described in the above-mentioned three documents in detail, as well as in the present specification (see, page 16, lines 16-23). By means of such a method, we identified peptide "690-698" as an antigen peptide, which is described in Example 4 at page 37, lines 12-15 of the present specification.

5.1.7. With regard to a tumor antigen peptide restricted to HLA antigen lacking "rule" in the amino acid sequence, it could be identified according to the method described in Example 4 of the present specification. That is, from a cDNA encoding a tumor antigen protein, clones of various length were prepared using Deletion Kit and analyzed the activity by measuring the amount of IFN-γ produced by CTLs as mentioned above. Peptide fragments of 8-12 amino acids were then synthesized based on the sequence of a clone having activity, and allowed to contact with cells for assay to determine whether of not the synthetic peptide fragments have the activity of binding to HLA antigen and being recognized by CTLs, as claimed in claim 7. After the series of procedures, there obtained three tumor antigen peptides corresponding to amino acid sequences "736-744", "749-757" and "785-793". One ordinary skilled in the art could identify any tumor antigen peptides by following the procedures described in

Example 4 involving "deletion".

5.1.8. As mentioned above, once a "tumor antigen protein" has been identified, one ordinary skilled in the art could identify tumor antigen peptides as recited in claims 7 and 8 on the basis of the known techniques regarding the length and motif of peptides capable of binding to MHC class I antigen, guidance and working examples in the present specification. Accordingly, the peptides as the subject matters of claims 7 and 8 are described in the specification to such an extent to enable one ordinary skilled in the art to make and use the same.

5.2. Claims 6-9 and 12-13 are novel over Nakao et al

5.2.1. I am familiar with the cited Nakao et al document, which reports the results of research work conducted in my office under my supervision. The results are those obtained prior to the cloning or identification of SART-1. It is my conclusion that Nakao et al did not anticipate the tumor antigen peptide derived from SART-1 on the basis of the facts below.

5.2.2. The Examiner takes the position that the tumor antigen peptide of the present invention and the antigen peptide of Nakao et al are identical because the both peptides are originated from KE-4 and recognized by KE-4CTL; however, this is not pertinent. That is, there are many tumor antigens which are distinct from SART-1 and yet expressed on KE-4 and recognized by KE-4CTL. We have so far identified such tumor antigens, namely, SART-2 (Nakao, M. et al, *J. Immunol.*,**164**, 2565 (2000)) and SART-3 (Yang, D. et al, *Cancer Res.*,**59**: 4056(1999)), which are distinct from each other and also from SART-1 in terms of structure.

5.2.3. Further, the subject matter as claimed in the present application is "isolated tumor antigen protein" and "isolated tumor antigen peptide", while Nakao et al do not describe such an "isolated" protein or peptide. Examiner pointed out that Nakao et al teach a peptide antigen expressed on SCC from KE-4 tumor cells specifically making reference to Fig. 3 on page 4251. Although the said Fig. 3 indicates the presence of a substance having activity in fraction No. 23, there are no evidences showing that the said fraction contains a single

protein/peptide, much less SART-1 of the present invention.

5.2.4. It is well known in the art that HPLC, when conducted under the conditions set forth in Nakao et al, gives peaks each containing plural peptides. Actually, it was technically very difficult for us to isolate and identify tumor antigen protein or peptide from the active fraction No. 23. We then used the "expression cloning technique" and succeed in the isolation and identification of SART-1 after continuous endeavors. It would be objectively understood that the active peak (No. 23) corresponds to a mixture of peptides of unknown structure, which is clearly distinct from the isolated tumor antigen protein or peptide of the present invention.

6. In summary, it is my conclusion that the peptides as the subject matters of claims 7 and 8 are described in the specification to such an extent to enable one ordinary skilled in the art to make and use the same, and that, on June 7, 1996, Nakao et al did not anticipate the tumor antigen peptide derived from SART-1.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

Date: _____, 2001

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Kyogo Itoh, M.D., Ph.D.

CURRICULUM VITAE

Kyogo Itoh, M.D., Ph.D.

Title and Affiliation:

Primary appointment: Professor and Chairman, Department of Immunology, Director of Kurume University Research Center for Innovative Cancer Therapy, Kurume University School of Medicine, Kurume, Fukuoka 830, Japan.

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Education:

Tohoku Univ. School of Medicine, Sendai, Japan, Ph.D. 1981, Immunology

Hirosaki Univ. School of Medicine, Hirosaki, Japan, M.D., 1974, Medicine.

Academic and Professional Appointments:

1998-present, Director of Kurume University Research Center for Innovative Cancer Therapy.

1992-present, Professor and Chairman, Department of Immunology, Kurume University School of Medicine, Kurume, Fukuoka 830, Japan.

1995-present, Adjunct Professor, Department of Immunology, The University of Texas, M. D. Anderson Cancer Center, Houston, Texas, U.S.A.

1992-1995, Adjunct Associate Professor, Departments of Immunology and General Surgery, The University of Texas, M. D. Anderson Cancer Center, Houston, Texas, U.S.A.

1990-1992, Associate Immunologist and Associate Professor of Immunology (Tenure),

Department of Immunology (General Surgery), and Chief of the TIL Core Lab, The University of Texas, M.D. Anderson Cancer Center, Houston, TX.

1990, Assistant Immunologist and Assistant Professor, Department of Immunology (General Surgery), and Chief of the TIL Core Lab, The University of Texas M. D. Anderson Cancer Center, Houston, TX.

1987-1990 Assistant Immunologist and Assistant Professor, Department of General Surgery (Immunology) and Chief, TIL Core Lab, The University of Texas M. D. Anderson Cancer Center, Houston, TX.

1987-1992 Member of the Graduate Faculty, Graduate School of Biomedical Sciences, The University of Texas Health Science Center at Houston, Houston, TX.

1986-87 Visiting Scientist, Department of General Surgery (Immunology), The University of Texas System Cancer Center, M.D. Anderson Hospital and Tumor Institute, Houston, TX.

1985-86 Postdoctoral Fellow, Department of General Surgery (Immunology), The University of Texas System Cancer Center, M.D. Anderson Hospital and Tumor Institute, Houston, TX.

1984-85 Research Associate, Departments of Surgery and Immunology, The University of Alabama at Birmingham, Alabama.

1978-88 Senior Instructor, Department of Microbiology, Tohoku University School of Dentistry and Medicine, Sendai, Japan.

1974-78 Surgeon, The Second Department of Surgery, Hirosaki University School of Medicine, Hirosaki, Japan.

1974-75 Surgeon, Division of Surgery, Misawa Central Hospital, Misawa, Japan.

Editorships and Editorial Board Memberships

Associate editor for J. Immunotherapy (1997-)

A member of editorial board for International Journal Clinical oncology(1996-)

Society Memberships:

The American Association of Immunologists (1987-present)
The American Association for Cancer Research (1988-present)
The American Society of Clinical Oncology (1990-present)
The Japanese Society for Immunology (1978-1984; 1992-present)
The Japanese Cancer Society (1979-1984; 1992-present)
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Kyogo Itoh, M.D., Ph.D.

a. Published and accepted articles in refereed journals:

1. Itoh, T., Murakami, T., Shioya, A., Itoh, K., Inoue, S., Itoh, S., Konn, M., and Oh-Uchi, K. A Case of lymphangioma in the descending colon. (Jp.) Clin. Surgery, *32:* 515-518, 1977.

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